## REMARKS

Claims 13-24 are pending herein and stand rejected. Claim 13 has been amended such that it is internally consistent. Specifically, claim 13 was amended to specify that individual components of the claim such as PSA, for example, are antigens over-represented on the prostate gland. Also, claim 13 has been amended to clarify that the active ingredient may comprise a nucleic acid that generates the antigen or antigens. Thus, the amendment to claim 13 is introduced for clarification and not in response to any of the rejections set forth in the Office action mailed 11 October 2000.

Formal Matters

The Office action suggests that Applicant should amend the first line of the specification to update the status of the priority documents. Amendment to the first line in the application is respectfully requested herein.

The Office action also required that the Title of the invention and the Abstract of the disclosure should be amended to conform with the claimed subject matter. Applicant has amended the Title of the invention and the Abstract of the disclosure so that they conform with the claimed subject matter.

Rejection of Claims 13 and 17-24 for Alleged Lack of Written Description

Claims 13, 27-24 are rejected under 35 U.S.C. § 112, first paragraph because the terms "over-represented antigens" and "nucleic acid sequences" allegedly do not meet the written description requirement. Applicants respectfully traverse the rejection.

The written description guidelines set forth in the Federal Register, Vol. 66, No. 4, 5 January 2001, state that a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. The guidelines also state that the Examiner has the initial burden of presenting by a preponderance of evidence why a person of ordinary skill in the art would not recognize in an

Applicant's disclosure a description of the invention defined by the claims. Also, the guidelines note that an adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.

It is believed that the Office action does not establish a *prima facie* case for lack of written description. Applicant asserts that a person of ordinary skill in the art would recognize a description in the specification of the invention defined by the claims.

With respect to "over-represented antigens," it is noted that claim 13 has been amended such that antigens over-represented in the prostate gland include an immunologically reactive portion of PSA, PSMA or an immunologically effective portion thereof, or PAP or an immunologically reactive portion thereof, mixtures of the foregoing. As described above, claim 13 was amended to provide internal consistency for the term "antigen." Thus, claim 13 was not amended to overcome a written description rejection because the specification provides a written description of the claimed "over-expressed antigens."

In particular, on page 7, line 21 to page 8, line 5, the specification provides a description of the antigen PAP. In addition, on page 8, line 10 to page 9, line 8, the specification provides a description for the antigen PSA. Furthermore, on page 9, lines 9-27, the specification provides a description of the antigen PSMA. The specification provides methods for preparing the antigens on page 10, line 9 to page 12, line 2. Methods for preparing immunologically reactive portions of the antigens by recombinant expression techniques and chemical synthetic techniques is set forth in the specification on page 12, lines 3-23. Hence, the specification sufficiently describes the "over-expressed antigens" enumerated in claim 13.

With respect to the term "nucleic acid sequences," it is noted that claim 13 was amended to provide internal consistency and to clarify that the nucleic acid expressed an enumerated antigen. The amendment was not introduced to overcome a written description rejection because the specification provides a written description for "nucleic acid sequences" of claim 13. The specification describes the nucleic acids of claim 13 on page 6, line 21 to page 7, line 14. In

addition, the specification on page 16, line 24 to page 17, line 4, describes how DNA encoding polypeptides such as PAP, PSA, PSMA, or portions of these may be administered to a subject by way of a viral expression vector. Hence, the specification demonstrates that Applicant plainly had possession of "nucleic acid sequences" as set forth in claim 13.

The Office action notes that nucleic acid sequences are not disclosed in the specification for the antigens. It is respectfully submitted that nucleic acid sequences for the antigens are not required because the nucleic acid sequence of the antigens is not claimed. Also, the specification refers the skilled artisan to nucleic acid sequences for antigens that were already publicly disclosed before the filing date of the application. For example, the specification refers the skilled artisan to the nucleic acid sequence of PAP on page 8, lines 1-5 and of PSA on page 9, lines 9-17.

Therefore, the specification provides an adequate written description for the terms "over-represented antigens" and "nucleic acid sequences." Accordingly, Applicant respectfully request that the rejection of claims 13 and 17-24 under 35 U.S.C. § 112, first paragraph, for lack of a written description be withdrawn.

Rejection of Claims 13-24 Under 35 U.S.C. § 112 for Alleged Lack of Enablement

Claims 13-24 were rejected in the Office action under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for "over-represented prostate-specific antigen" and "immunologically effective portions thereof." The rejection is respectfully traversed.

As noted in the previous section of this response, claim 13 is directed to specific over-represented prostate-specific antigens. Specifically, the antigens include an immunologically reactive portion of human PSA, human PSMA or an immunologically effective portion thereof, PAP or an immunologically reactive portion thereof, and mixtures of the foregoing. Applicant extends gratitude to the Examiner for clarifying that the specification is enabling for full-length PSA, PSMA, and PAP. Applicant asserts that the specification is also enabling for

immunologically reactive portions of those antigens as well as nucleic acids that generate one or more of those antigens *in situ*. Specifically, the following demonstrates that (1) the specification provides sufficient guidance and working examples that enable the skilled artisan to practice the claimed subject matter; (2) the claimed methods are credible and are not unpredictable; and (3) methods of utilizing immunologically effective portions of the antigens PAP, PSA, and PSMA and nucleic acids that generate one or more of those antigens *in situ* would not require undue experimentation.

The Specification Provides Guidance and Working Examples that Enable the Claimed Subject Matter

The specification teaches the skilled artisan how to make, formulate, and administer full-length antigens, immunologically reactive portions thereof, and nucleic acids encoding one or more of those antigens *in situ*. On page 10, line 9 to page 12, line 2, the specification teaches the skilled artisan how to prepare antigens. On page 12, lines 3-23, the specification teaches the skilled artisan how to generate immunologically effective portions of the antigens. Examples of generating the antigens *in situ* by an expression system is set forth on page 6, line 21 to page 7, line 14. On page 16, line 24 to page 17, line 4, the specification provides an example of a viral expression vector for the claimed nucleic acids, and teaches "naked" DNA may also be utilized.

The specification also provides a description of compositions by which the claimed antigens may be formulated on page 14, line 15 to page 17, line 4. Furthermore, the specification on page 17, line 5 to page 19, line 20 provides the skilled artisan with a description of how to administer antigens and nucleic acids of the claimed methods.

Thus, one of ordinary skill in the art may practice the claim methods in view of the extensive teachings provided by the specification.

Claimed Methods Are Credible and Are Not Unpredictable

The claimed methods are credible and are not unpredictable because the (1) the claimed methods have been shown to elicit an immune response in human subjects; (2) documents cited in the Office action demonstrate efficacy of the claimed methods; and (3) the Examiner states that the skilled artisan would have reason to believe the claimed methods are not unpredictable.

Claimed Methods Elicit an Immune Response in Human Subjects

Evidence of such immune responses has been entered in the record of the patent applications to which the above-identified patent application claims priority by way of declarations. Copies of these declarations are appended herewith as Exhibit B. Included with Exhibit B is a paper filed in Application Serial No. 08/105,444 on 7 May 1998 which summarizes the data set forth in the declarations. Taken as a whole, the declarations submitted report the results of five clinical mini-trials and a study in a murine model using recombinant human PSA, which has been trademarked Onco Vax P™. T-cell responses were obtained in patients in all studies and the fifth clinical study demonstrated dramatic and consistent T-cell responses. The evidence also demonstrates that T-cell response is correlated with an antitumor effect. The success of the claimed methods with the antigen PSA predicts a similar efficacy with the antigens PSMA and PAP, as well as immunologically reactive portions of the antigens and nucleic acid that generates one or more of the antigens *in situ*.

Cited Documents Demonstrate Efficacy of the Claimed Methods

The Office action cites two documents, Spitler (*Cancer Biotherapy* **10**:1-3 (1995)) and Hodge *et al.* (*International Journal of Cancer* **63**:231-237 (1995)), which allegedly state the claimed methods would be unpredictable. However, these documents demonstrate that the claimed methods are credible and not unpredictable *when read in their entirety.*

In particular, Spitler states that

> [I]nvestigators working in the university setting using vaccines to treat cancer patients have occasionally seen clinical responses to this therapy, which at times has been dramatic. Almost everyone working in this field has had the experience of seeing a dramatic

> regression of metastatic disease following vaccine therapy. There are numerous published reports of these responses as well as unpublished observations of individual investigators.

Spitler concludes the article by stating:

> Now that the active components to the vaccine have been identified and purified, we are approaching the stage in technology where the interferons were in the beginning of the 1980's. The decade of the vaccine may finally have arrived!

Hence, when read in its entirety, Spitler does not support the Examiner's contention that the successful use of antitumor vaccines would not be credible to a skilled practitioner or that undue experimentation is required to practice the claimed methods.

In addition, Hodge reports a rhesus monkey study showing that a recombinant vaccinia virus that expresses human PSA successfully generates a humoral and cellular immune response without showing any toxicity. At page 236, Hodge states "we have shown that it is possible to mount humoral and cellular immune responses specific for PSA in rhesus monkey after immunization with a recombinant vaccinia virus expressing PSA." One skilled in the art reading Hodge would be left with the conclusion that antitumor vaccines are viable therapeutics for the treatment of cancers and that PSA is an attractive candidate for such therapeutic modalities.

In summary, the two documents cited by the Examiner themselves support the position that a skilled artisan would not find the disclosure of the specification in any way incredible, that many antitumor vaccines have been tested and that the skilled artisan would have a reasonable expectation of success when practicing the teachings of the specification. Hence, efficacious results of the claim methods are credible and are not unpredictable.

Admission that the Claimed Methods Are Credible and Not Unpredictable

The fact that the claimed methods are credible and not unpredictable is further bolstered by the position taken in the Office action to which this is a response:

> It would have been obvious to the ordinary artisan to use PSMA in patients with metastatic prostate tumors and/or patients who have had the prostate tumor removed surgically to elicit antitumor responses in order to treat said cancer

patients. Also, it would have been obvious to the ordinary skilled artisan to select portions, particularly extracellular portions of PSMA to stimulate antitumor responses. *From the teachings of the references known in the prior art it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention* (emphasis added). Office action mailed 11 October 2000, page 11, second paragraph.

Hence, it appears that eliciting an antitumor response using full-length polypeptides, portions of the polypeptides, and nucleic acid to express the polypeptides would not in the Examiner's own view be unpredictable. Thus, the claimed methods are credible and not unpredictable.

Any Experimentation Is Not Undue

As described above, the specification provides extensive guidance and examples for practicing the claimed subject matter. In addition, the claimed methods have actually been shown to be effective for eliciting an immune response in human subjects. The teachings of the specification in conjunction with the efficacy of the claimed methods demonstrate that any experimentation required for practicing the claimed embodiments would not be undue.

The law allows for the level of repetition required for practicing the claimed methods. For example, in *In re Wands*, 8 USPQ.2d 1400 (Fed. Cir. 1988), the Court of Appeals for the Federal Circuit found that a claim reciting the use of any high affinity IgM was fully enabled despite the fact that the claim read on the use of nearly an infinite number of particular antibodies. In the situation addressed in *In re Wands*, it would require an enormous amount of effort to practice every embodiment, but only a minimal amount to practice any one embodiment. Patents such as these have not been rejected and have been upheld as being valid despite the enormous amount of experimentation that would be required to practice every embodiment of the claimed invention because only some experimentation is required to practice any particular embodiment.

The specification teaches all of the steps required for practicing the proven claimed methods, and all that remains is repetition of these teachings to practice the scope of the claims.

As described above, the claimed methods have been carried-out according to the teachings of the specification using PSA as an antigen and result in an immune response. Repeating vaccine studies for different antigens, including full-length polypeptides, portions of those polypeptides, and nucleic acids that express the foregoing polypeptides *in situ*, is routine. The routine nature of such vaccine studies is exemplified in the Spitler and Hodge documents cited in the Office action, as described above.

Thus, the claimed methods can be easily practiced by a person of ordinary skill in the art with only routine experimentation. Accordingly, any experimentation required for practicing the claimed methods would not be undue.

In view of the foregoing, Applicant requests that the rejection of claims 13-24 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claim 24 Under 35 U.S.C. § 112, First Paragraph

Claim 24 is rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly does not contain a written description for the claimed subject matter. The rejection is respectfully traversed.

The subject matter of the claim need not be described literally (*i.e.*, using the same terms or in *in haec verba*) in order for the disclosure to satisfy the written description requirement. MPEP section 2163.02. Claim 24 is directed to the application of the method of claim 13 to a subject afflicted with metastatic prostate cancer and/or where the subject has been surgically treated to excise the tumor but is at risk for reoccurrence. The specification provides support for such subjects on page 4, line 6 to page 5, line 3, page 17, lines 5-16, and page 18, line 30 to page 19, line 10. Thus, the specification provides a written description for the subject matter of claim 18. Accordingly, it is respectfully requested that the rejection of claim 24 be withdrawn.

Rejection of Claims 13 and 20-24 Under 35 U.S.C. § 112, Second Paragraph

Claims 13 and 20-24 stand rejected under 35 U.S.C. § 112, second paragraph, because the term "over-represented antigens" is allegedly indefinite. The rejection is respectfully traversed.

As noted above, claim 13 specifies that the term "antigen over-represented in the prostate gland" is directed to an immunologically reactive portion of PSA, PSMA or an immunologically effective portion thereof, or PAP or an immunologically reactive portion thereof. In addition, the specification provides a definition for the term "over-represented" on page 5, lines 18-23. Because claims 20-24 directly or indirectly depend from claim 13, these claims are also definite with respect to the term "over-represented antigens." Accordingly, it is respectfully requested that the rejection of claims 13 and 20-24 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection of Claims 13-24 under 35 U.S.C. § 103(a)

Claims 13-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spitler (U.S. patent No. 5,738,867) in view of Israeli *et al.* (U.S. patent No. 5,538,866) and documents disclosed on pages 10-19 of the specification of the instant application. The rejection is respectfully traversed.

Claims 13-24 are directed to a method of eliciting an immune response in a subject against an antigen over-represented in prostate. The specification describes an inventive feature of the claimed subject matter on page 4, lines 11-22:

> While the prior art suggests the use of antigens uniquely associated with tumor tissue as components of antitumor vaccines, there appears to be no suggestion to use antigens which are uniquely represented on host tissue for the tumor. Since the prostate is not an essential organ, elimination of the prostate gland, which may be a concomitant effect of the vaccines of the invention, does not adversely impact the general health of the subject. Thus, prostate cancer offers a unique opportunity for treatment with vaccines which characterize *the host organ itself, rather than the malignant or metastatic nature of the cells per se* (emphasis added).

Thus, an inventive feature of the claimed methods is that the problem of treating prostate cancer had never before been addressed by eliciting an immune response against host prostate tissue.

The Cited Documents Do Not Result In The Claimed Methods

Claims 13-24 have an inventive step over the cited documents because the documents provide no suggestion of eliciting an immune response in a subject against host prostate tissue.

Spitler discusses the use of tumor-associated antigens in vaccines for the treatment of cancers. Spitler does not suggest mounting an immune response in a subject against antigens that are present in host prostate tissue.

Israeli discusses the isolation of nucleic acid encoding PSMA. Also, Israeli discusses *ex vivo* production of antibodies against PSMA. Israeli does not cure the defects of Spitler because it also fails to suggest a method for eliciting an immune response in a subject against host prostate tissue. The documents cited in the specification on pages 10-19 discuss general methods of delivering antigens of interest to stimulate antitumor responses. However, none of these documents cure the defects of Spitler and Israeli because they fail to discuss methods for eliciting an immune response in a subject against antigens present in host prostate tissue.

Hence, the cited documents do not result in the claimed subject matter because the combination of documents does not teach or suggest a method for eliciting an immune response against host prostate tissue.

There Is No Motivation To Combine The Cited Documents

Even if the cited documents resulted in the claimed subject matter, which they do not, there is no motivation to combine the documents. The Court of Appeals for the Federal Circuit has stated that there are three possible sources for a motivation to combine documents: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998).

It is respectfully submitted that there is no motivation to combine the cited documents in view of the standards set forth in *In re Rouffet*. As noted above, Spitler addresses methods for eliciting an immune response against cancer tissue, and does not appreciate the concept of mounting an immune response against host prostate tissue. Israeli also fails to suggest the a

method for mounting an immune response against host prostate tissue. None of the other cited documents address such a concept. Thus, it does not appear that the prior art provides a motivation to combine the cited references.

Because the cited documents also do not result in the claimed subject matter, it is respectfully requested that the rejection of claims 13-24 under 35 U.S.C. § 103 be withdrawn.

Rejection of Claims 13-24 for Alleged Obviousness-Type Double-Patenting

Claims 13-24 of this application have been rejected under the judicially-created doctrine of obviousness-type double-patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 5,925,362. Applicants respectfully request that this rejection be held in abeyance until the above-identified issues have been resolved.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 204372000301. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: April 11, 2001

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## EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Claims:**

13. (Amended) A method to elicit an antitumor immune response to prostate tumors in a subject, which method comprises

administering to said subject at least one active ingredient formulated for administration to said subject,

wherein said active ingredient comprises or expresses at least one antigen over-represented in the prostate gland or an immunologically effective portion thereof,

wherein [said active ingredient] said antigen is an immunologically reactive portion of human prostate-specific antigen (PSA); or

human prostate-specific membrane antigen (PSMA) or an immunologically effective portion thereof; or

prostatic acid phosphatase (PAP) or an immunologically reactive portion thereof; or mixtures of the foregoing; or

wherein said active ingredient comprises [is] a nucleic acid that generates said antigen or antigens *in situ*.